Comments and suggestions regarding the planned implementation of the 'Advanced Therapies' Regulation (EC) No 1394/2007

The RNA Therapeutics Stakeholder Group

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1 Appraisal and summary of concerns

The present comments and suggestions are drafted by a considerable number of stakeholders from academia, scientific consortia as well as small and medium-sized enterprises devoted to various aspects of development of advanced therapies (detailed list in **Annex 2)**. Although the stakeholders greatly appreciate the European Commissions efforts to improve regulation of authorization, supervision and pharmacovigilance of advanced therapy medicinal products they are concerned that the Regulation will seriously compromise the further development of several classes of highly promising medicinal products.

- According to Definitions 2.2.1 RNA-based medicinal products are classified as gene therapy medicinal products. Regulatory rules for gene-therapeutic medicinal products were primarily developed to improve safety of viral gene transfer, which is associated with integration into the host genome and carries the risk of vertical transmission. Accordingly, regulatory requirements include the evaluation of oncogenic and tumorigenic potential in relevant *in vivo* models, reproductive and developmental toxicity studies, integration site studies, clinical data regarding biodistribution into gonads as well as a range of safety studies including neoplastic proliferation due to insertional mutagenicity. As detailed in Annex 1 none of these risks applies to RNA-based medicinal products. RNA does not integrate into the host genome and is neither oncogenic.

- Application of requirements developed for viral gene transfer will multiply the costs for RNA-based medicinal products and will put the future of SMEs in the field in jeopardy. The clinical development of DNA-based gene transfer owing to the difficulties to finance increased expenditures has almost come to halt in the last years. We are alarmed that application of the Regulation to RNA-based medicinal products will retard or even prevent their development while not providing any significant advantage for the safety of the treated patients. Moreover, we are concerned about differences in regulatory requirements between the EU and other countries. If the EU increases regulatory hurdles not based on strong scientific arguments this will compromise the European habitat conditions for development of innovative products.

2 Summary of suggestions for changes

Based on the detailed comments in the **Scientific Annex** we ask for following changes:

a) RNA based medicinal product classes including but not limited to non-viral RNA vaccines, adjuvants, siRNA and aptamers, shall be explicitly excluded from the "Gene therapy" classification of the regulation.

b) Such RNA based medicinal product classes, which are synthetically or enzymatically produced in vitro, are designated for direct in vivo application and do not apply to the definition of somatic cell therapy should be further on regarded as Chemical Entities as exemplified by previous approvals for representatives of this class (Vitravene™ Macugen™) and should not be a subject of the advanced therapy Regulation.

c) RNA based medicinal product classes shall explicitly be excluded from regulatory requirements outlined in chapter 2.4.2 of the regulation, such as genotoxicity, carcinogenicity, reproductive and developmental toxicity studies as well as genome integration studies as these address specific features of classical gene therapy but do not apply to RNA.

d) Analogously, RNA based medicinal product classes shall explicitly be excluded from clinical data requirements listed in chapter 2.5.2, such as analysis of biodistribution into the gonads and safety studies. Also these refer to peculiar risks associated with classical gene therapy, but not with RNA administration.

e) Rather, we believe that a risk analysis approach as already suggested in chapter 2.1 of the Regulation combined with mode of action based risk identification strategies outlined in chapter 4.1. of the "Guideline On Strategies To Identify And Mitigate Risks For First-In Human Clinical Trials With Investigational Medicinal Products" (EMEA/CHMP/SWP/28367/07) may comply best with the peculiarities of such RNA based novel therapies

3. Expression of support

The stakeholders support an opinion featured in a commentary submitted independently to the Commission that the definition "Gene therapy" and specific regulatory requirements for gene therapy should not apply for plasmid based recombinant vaccines.

Annex 1 Detailed statements

In the regulation (EC) No 1394/2007 on advanced therapy medicinal products ("the Regulation") specific rules are defined, that concern the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue engineering). This regulation will apply from 30 December 2008. As part of the implementation of regulation No 1394/2007, the European Commission intends to revise and adapt Part IV, Annex I to the Directive 2001/83/EC.

The following comments and suggestions originate from a considerable number of different stakeholders (listed in Annex I) comprising academic experts in the field, small and medium sized enterprises as well as prominent non-profit research organizations dealing with different aspects of advanced therapies ("The Stakeholders"). Whereas the Stakeholders highly appreciate several aspects of the regulation, such as the establishment of a Committee for Advanced Therapies (CAT) within the EMEA, there are major concerns regarding some other aspects of the Regulation.

A central concern of the Stakeholders is the definition of gene therapy medicinal product which is outlined in chapter 2.2.1 of the Regulation, which is linked to specific requirements concerning the extent of clinical and non-clinical data.

According to the Regulation a Gene therapy medicinal product is defined as a medicinal product

- *that contains or consists of a nucleic acid sequence used in or administered to human beings, in vivo or ex vivo, with a view to regulating, repairing or replacing a targeted genetic sequence; and*

- *whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence.*

A number of specific requirements regarding non-clinical and clinical data are listed in chapter 2.4.2 or chapter 2.5.2 of the Regulation, respectively. for medicinal products, that fullfil this definition.

Requirements include among others

- **evaluation of oncogenic and tumorigenic potential in relevant models,**
- **reproductive and developmental toxicity studies,**
- **integration site studies,**

- **clinical data regarding biodistribution into gonads as well as a range of safety studies including data about neoplastic proliferation due to insertional mutagenecity.**

The Stakeholders are concerned that the definition of gene therapy medicinal products within the regulation is extremely broad, comprising a heterogenous collectivity of different medicinal product classes with distinct individual safety and mode of action profiles and peculiarites. Whereas the studies listed in chapter 2.4.2 and 2.5.2 are without doubt meaningful for a number of classical gene therapy approaches e.g. addressing gene transfer with retroviral, lentiviral or adenoviral vectors, they are clearly neither scientifically nor clinically justified for other medicinal approaches such as transfer of non-replicating polynucleotide RNA or siRNA, which are most likely non-intentionally also covered by the definition.

A particular criticism is that RNA based medicinal product classes are not explicitly excluded from the gene therapy definition.

An important feature crucial for clinical safety issues is that RNA based medicinal products bear no significant risk for integration into the genome. This is in contrast to some recombinant viral medicinal products that have the risk of drug accumulation due to a sustained expression of encoded gene products and the risk of integration into the host genome, thereby promoting malignant transformation by activating proto-oncogenes or inactivating onco-suppressors [1]. Furthermore DNA, when integrated into the chromosomal DNA of germ line cells could lead to vertical transmission. Importantly, all known mechanisms by which foreign nucleic acids can integrate into the genome of an animal cell (e.g. recombination) do not apply for RNA based molecules[2]. Due to the lack of capacity to integrate into genomes there is also no risk for long-term persistence of RNA based medicinal product classes. It is well established that medicinal products based on RNA are of transient nature and are cleared from the organism mainly by degradation by nucleases that are abundant in the extra- and intracellular space[3].

The Stakeholders are concerned that the Regulation would enhance regulatory requirements for a number of highly promising, emerging clinical applications of RNA[4] while not providing any significant advantage for the safety of the treated patients. This would slow down or even prevent clinical translation of such substances and unnecessarily discriminate against European researchers and companies as RNA based approaches are not considered as gene therapy in competing countries and regions of the world including the USA.

RNA molecules can be applied as medicinal products

- to transiently silence genes of interest (RNA interference),
- to modify gene specific splicing events (RNA repair),
- to induce antigen specific immune responses (RNA vaccines)
- to augment immunity (RNA adjuvants e.g. Poly I:C)
- to bind receptors or ligands involved in disease mechanisms (Aptamers)

In the past years, a large amount of non-clinical data and a considerable number of clinical studies have been performed demonstrating an excellent safety profile of RNA-based therapeutic strategies. These include published clinical trials as well as hitherto unpublished data generated by some of the Stakeholders. RNA based vaccines, for example, which entered clinical testing nearly one decade ago were shown to be very well tolerated[5-10]. RNA vaccine based medicinal products are either used for ex vivo transfection of dendritic cells or directly injected as naked RNA vaccines in vivo. Taken together published clinical trials, so far 131 patients have been treated in vaccination protocols using RNA-based medicinal products. Only one patient developed a toxicity > grade I (flu like symptoms, grade II). Generally, the side effects were restricted to grade I local erythema at the injection site and grade I flu like symptoms. A transient increase in anti-nuclear-antibodies was seen in three patient. Otherwise no signs of autoimmunity have been observed so far.
Similarly, a number of clinical trials with Aptamers as well as a wide range of preclinical studies and first clinical trials with siRNA therapeutics indicate an excellent safety profile also for other RNA-based medicinal product classes[11-15]. Many of these approaches are based on synthetic oligonucleotides. In fact, there is historic precedence for the regulation of oligonucleotides as chemical entities in Europe with the approval of Vitravene™, an antisense oligonucleotide for treatment of cytoMegalovirus retinitis (CMV), and Macugen™, a pegylated aptamer approved for treatment of age-related macular degeneration (AMD).
We believe that RNA-based therapeutics have a great potential to provide solutions in different disease areas with high medical need including infectious, metabolic and cardiovascular diseases as well as cancer. RNA based medicinal products can be rapidly produced and easily purified. Production costs are considerably lower than for polypeptide based medicinal products. This, together with their nucleotide sequence based target specificity provides an excellent basis for future individualized therapies. A number of young biotechnology companies mainly funded by venture and public capital are devoted to develop and implement such innovative treatment modalities. However, the field of RNA based medicinal products is young and highly vulnerable. It is important that investments in this field are neither endangered by high development hurdles nor by a misleading public perception. Due to the fatal events associated with adenoviral and retroviral gene transfer the term "Gene therapy" is burdened with a negative public perception[16-18]. The broad

classification of different nucleic acids based medicinal products as gene therapy endangers their public acceptance and will compromise investments necessary for the development of the field.

We propose that the definition "Gene therapy" should be limited to nucleic acids based medicinal products, which are able to integrate into the human genome thereby generating unique safety concerns.

RNA based medicinal product classes neither integrate into the genome, nor induce genome sequence alterations eo ipso. The fact that RNA based therapeutic approaches such as RNA interference is able to specifically modulate gene transcription and translation is not a characteristic feature of gene therapy as the vast majority of medicinal products affect gene transcription and gene expression in a very defined manner (e.g. hormones, antibodies, kinase inhibitors etc.). In this context, it is important to realize and accept, that a medicinal product based on a viral vector encoding a sh-RNA for gene silencing has a profoundly different risk profile as compared to the corresponding non-viral, siRNA based medicinal product[19;20].

Moreover, it is critical that the progress of clinical translation in the field is not slowed down by unsubstantiated regulatory mechanisms. Most of the requirements listed in the chapters 2.4.2. and 2.5.2 of the Regulation (i.e. analysis of oncogenic and tumorigenic potential in relevant models, reproductive and developmental toxicity studies, integration site studies, clinical data regarding biodistribution into gonads as well as a range of safety studies including data on neoplastic proliferation due to insertional mutagenecity) are scientifically and clinically not justified, but are time consuming and cost intensive. Application of these requirements would multiply the costs for RNA-based medicinal products while not providing any significant advantage for the safety of the treated patients. During the last years clinical development of DNA-based gene transfer due to the difficulties to finance came to a halt. We are alarmed that application of the proposed regulation to RNA-based medicinal products will severely compromise the development of these highly promising drugs. We are also concerned about different regulatory hurdles between the EU and the US. If only the EU increases the requirements and if this is not based on strong scientific arguments these rules will compromise the habitat conditions of the EU for development of innovative products.

For the reasons discussed above we appeal that therapeutic strategies based on non-replicating RNA medicinal products are neither defined nor considered as gene therapy.
Accordingly, we appeal that advanced therapeutic strategies based on application of RNA transfected or RNA loaded cells should also not be regarded as gene therapy.

Rather, we believe that a risk analysis approach as already suggested in chapter 2.1. of the Regulation combined with mode of action based risk identification strategies, which are described in chapter 4.1. of the "Guideline On Strategies To Identify And Mitigate Risks For First-In Human Clinical Trials With Investigational Medicinal Products" (EMEA/CHMP/SWP/28367/07) may be appropriate and sufficient to deal with the individual characteristics of these novel therapies.

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Annex 2 List of Stakeholders

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Prof. Jonathan Austyn, Coordinator of **"DC-THERA FP6 Network of Excellence in Dendritic Cell Translational Immunology"** (http://www.dc-thera.org/), declares that the network is pleased to formally support the commentaries on the new EC/EMEA regulations (No 1394/2007) concerning the authorization, supervision, and pharmacovigilance of advanced therapy medicinal products.
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Prof. Dr. Dr. h.c. Ch. Huber, board chairman of the **"Cancer Immunotherapy"** consortium (CIMT, www.c-imt.org), declares that CIMT supports the commentaries on the new EC/EMEA regulations (No 1394/2007) concerning the authorization, supervision, and pharmacovigilance of advanced therapy medicinal products.
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